PhRMA

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BY MESSENGER

Dockets Management Branch (HFD-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE: Comments on FDA Draft Guidance on Fast Track Products – Section 112 of the FDA Modernization Act (FDAMA)
Docket No. 98D-0813 (63 Fed. Reg. 64093, November 18, 1998)

Dear FDA:

We are writing on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA) to provide industry comments on the above-referenced draft Fast Track Guidance. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives; our members invest over $24 billion a year in discovering and developing new treatments. For this reason, PhRMA and its members are keenly interested in Section 112 of FDAMA, which created a new statutory mechanism (Food, Drug, and Cosmetic Act Section 506) for facilitating the development and expediting the approval of drugs and biological products that demonstrate the potential to address unmet medical needs for serious or life-threatening conditions. This statutory provision codifies and expands FDA's existing programs for accelerated approval products in order to facilitate patient access to products that qualify for fast track designation and FDA approval.

The enclosed comments on FDA's November, 1998 draft guidance follow industry input on a recommended approach for implementing Section 112 that was provided March 31, 1998. We are pleased that the draft fast track guidance is generally consistent with the letter and spirit of FDAMA. The enclosed comments address the many respects in which the draft guidance comports with Section 112. The comments also discuss several important issues on which further guidance is needed to fulfill the goals of Section 112 and facilitate patient access to the valuable new treatments that qualify for fast track designation and FDA approval. These issues include:

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1. the duration of the requirement for advance submission of promotional materials for products receiving accelerated approval (comments p. 4);

2. clarification of FDA's intent to allow submission of portions of an application (p. 5);

3. clarification of the application of existing review programs to fast track products (p 6);

4. refinement of the timeframe within which FDA will respond to a request for fast track designation (p. 9);

5. amplification of FDA's intention to provide "timely" comments to a sponsor on proposed trial designs (p. 10); and

6. expansion of FDA's actions to promote awareness of fast track products and the development of surrogate endpoints (p. 10).

We hope that these comments prove useful. The PhRMA Fast Track Work Group is available at your convenience to answer any questions, or otherwise assist in assuring that this important provision is both timely and appropriately implemented.

Sincerely,

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Enclosure

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PhRMA

February 16, 1999

COMMENTS OF THE PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA

ON

FDA'S GUIDANCE FOR INDUSTRY ON FAST TRACK DRUG DEVELOPMENT PROGRAMS

DOCKET NO. 98D-0813

SUBMITTED TO THE DOCKETS MANAGEMENT BRANCH OF THE FOOD AND DRUG ADMINISTRATION

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $24 billion a year in discovering and developing new treatments, PhRMA companies are leading the way in the search for cures.

As pioneers in the discovery and development of new drugs for the treatment of serious and life-threatening conditions, PhRMA companies have a unique interest in the fast track drug development programs of the Food and Drug Administration (FDA) and FDA's implementation of section 112 of the FDA Modernization Act of 1997. Section 112 of the FDA Modernization Act codifies and expands FDA's existing programs for accelerated approval products by adding a new Section 506 to the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. § 356) and creating a statutory mechanism for

facilitating the development and expediting the approval of drugs and biological products that demonstrate the potential to address unmet medical needs for serious or life-threatening conditions.

FDA's new guidance on the Agency's fast track programs[1] implements section 112 in a manner that is generally consistent with the letter and the spirit of section 112. In particular, FDA's guidance (pp. 3-7) establishes appropriate criteria for determining whether a product qualifies for fast track designation. These criteria are consistent with existing FDA guidelines on what constitutes a serious or life-threatening condition and what constitutes a meaningful therapeutic benefit over existing treatments.[2] The guidance (pp. 9 & 15-16) also clearly distinguishes between fast track designation and accelerated approval. As provided in section 112 and noted in FDA's guidance (p. 15), a product with fast track designation may seek traditional approval based on data demonstrating an effect on a clinically meaningful endpoint or a well-established surrogate endpoint. Only those fast track products that seek accelerated approval

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[1] *See* 63 Fed. Reg. 64093 (Nov. 18, 1998) (announcing the availability of a guidance for industry entitled "Fast Track Drug Development Programs: Designation, Development, and Application Review").

[2] There does appear to be one typographical error on page 3 of the guidance, which could create some potential confusion. The final sentence of Section I states that the guidance addresses FDA's programs for drugs that demonstrate the potential to advance the treatment of "serious and life-threatening illnesses" (emphasis added). As the other sections of FDA's guidance make (continued...)

based on a surrogate or clinical endpoint that is "reasonably likely to predict clinical benefit" but cannot support traditional approval may be subject to post-approval requirements under section 112.

Notwithstanding the general adherence of FDA's fast track guidance to section 112, the guidance does not address several important issues on which further guidance is needed to fulfil the goals of section 112 and facilitate patient access to the valuable new treatments that qualify for fast track designation and receive FDA approval. Six issues in particular warrant further comment from FDA: (1) the duration of the requirement for advance submission of promotional materials for products receiving accelerated approval; (2) clarification of FDA's intent to allow submission of portions of an application; (3) clarification of the application of existing review programs to fast track products; (4) refinement of the timeframe within which FDA will respond to a request for fast track designation; (5) amplification of FDA's intention to provide "timely" comments to a sponsor on proposed trial designs; and (6) expansion of FDA's actions to promote awareness of fast track products and the development of surrogate endpoints. A more detailed discussion of each of these issues follows.

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clear, a product can qualify for fast track designation if it is intended for the treatment of a "serious or life-threatening condition." This reference should be corrected.

1. Advance Submission of Promotional Materials Following Approval

Under section 112 of the FDA Modernization Act, FDA may require the sponsor of a product that receives accelerated approval to submit promotional materials for the product at least 30 days prior to the sponsor's dissemination of the materials. FDCA § 506(b)(2)(B); 21 U.S.C. § 356(b)(2)(B). Congress has indicated that such advance submission of promotional materials should only be required when appropriate and "for a period of time necessary for the sponsor to demonstrate that it understands and will comply with the FDA's promotional material requirements." H.R. Rep. No. 105-310, at 56 (1997). In accordance with Congress' clear intent, when a sponsor has demonstrated a record of compliance with applicable promotional requirements, advance submission of promotional materials following accelerated approval becomes unnecessary and can be appropriately discontinued.

As a general rule, when FDA requires the advance submission of promotional materials, the requirement should end six months following accelerated approval, or sooner if phase IV studies are completed sooner. Once phase IV studies are finished and reported to FDA, no basis exists to distinguish an accelerated approval product from a product approved under traditional criteria, and FDA's ordinary rules on the submission of promotional materials should apply. *See* 21 C.F.R. § 314.81(b)(3)(i) (requiring submission of promotional materials at the time of initial dissemination).

Even when phase IV studies are not yet completed, six months provides a sufficient time for a sponsor to demonstrate its understanding of and compliance with pertinent rules and constraints for its promotional materials.

In most cases, requiring the advance submission of promotional materials for a longer period of time is not justified and would not constitute a sensible use of either FDA's or the sponsor's resources. Of course, FDA must retain the authority to require the continued advance submission of promotional materials for a sponsor who has not demonstrated a record of compliance. However, for a sponsor who has demonstrated compliance, little would be gained by FDA's continued advance review of the same or similar materials year after year. FDA, of course, retains its general authority to take enforcement action against false or misleading promotion, and that authority provides an appropriate safeguard against violative promotion without the administrative burdens of continued advance submission.

2. <u>Submission of Portions of an Application</u>

FDA's new guidance (p. 14) states that the Agency will accept pre-agreed portions of an application. At the same time, however, the guidance states that review will not necessarily commence prior to receipt of a complete application. We agree that FDA must reserve decision-making authority over its resources and discern the appropriate timing for initiating the review of each unique application. However, in the

interest of not discouraging sponsors from discussing presubmissions with the agency (recognizing that presubmissions can facilitate review in some cases), we would encourage the agency to amend subsection d on page 14 to state that "*The agency intends to make a reasonable effort, pending availability of resources, to initiate review of presubmissions prior to receipt of the complete application.*"

FDA should also make clear that the sponsor should set forth at the pre-NDA meeting its proposal regarding the content of components of an application that it plans to submit for FDA review. FDA's guidance (pp. 13-14) identifies several examples of portions of an application that it will ordinarily accept for submission. Additional examples should include appropriate subsections of components of an application, including the clinical pharmacology subsection of the clinical section and discrete subsections of the toxicology section. These subsections are often separate and distinct and reviewed by different FDA reviewers. They also may be available in advance of the rest of the larger section into which they fit.

3. <u>Review Programs for Fast Track Products</u>

FDA's guidance (pp. 12-16) discusses the various programs that may be considered for the review and approval of fast track products. This discussion can and should be clarified in three particular respects.

First, the guidance should be explicit that the regulatory requirement for further (post-approval) studies is limited specifically to products approved under the accelerated approval provisions, wherein 21 C.F.R. § 314.510 stipulates specifically that accelerated approval is subject to the requirement that the applicant study the drug further to verify and describe the clinical benefit of the product. This requirement is well understood and there are numerous precedents in place.

Second, the guidance should also be explicit (pp. 15-16) that its discussion of approval based on clinical endpoints other than survival or irreversible morbidity -- for example, in accordance with the three explanatory bullet points on page 16 -- applies solely to situations in which accepted, validated surrogate endpoints are not in hand. So, for example, drugs for hypertension, diabetes, or atherosclerotic cardiovascular disease are <u>not</u> encompassed by this provision since there are long-standing precedents for FDA's acceptance of validated surrogate endpoints for each of these diseases.

Third, the guidance should expand and clarify its discussion of the standard of evidence for fast track products seeking accelerated approval. FDA's guidance states (p. 11) that the standard of evidence applicable to "principal controlled trials" is set forth in 21 CFR 314.126, and refers to FDA's guidance on "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" (May 1998). The guidance also

discusses (p. 16) illustrative examples of clinical endpoints that could support accelerated approval. These important, but limited, statements could be expanded to provide clearer information on the standard of evidence of effectiveness for accelerated approval. For example, the illustrative clinical endpoints discussed on page 16 address clinical endpoints measuring short-term benefit and measuring lesser symptoms or signs of a disease, but do not address the situation of data on a long-term survival or irreversible morbidity endpoint that do not support traditional approval but might still be "reasonably likely to predict clinical benefit" and support accelerated approval under the standard set forth in section 112 of the FDA Modernization Act where no alternative therapy exists for a serious or life-threatening condition and post-approval confirmation studies will be performed We suggest the following section to address these points:

Standard of Evidence of Effectiveness for Fast Track Products:

The effectiveness of fast track products should be demonstrated, in principle, in the same manner as for other products. The regulatory basis of an adequate and well-controlled trial is well defined (21 CFR 314.126) and it provides sponsors with the opportunity to gather evidence of effectiveness using a valid comparison with a control. It is important for sponsors to note (including in the setting of fast track products intended for treatment of serious or life-threatening diseases) that the regulations recognize several options for the types of controls: (1) placebo concurrent control, (2) dose-comparison concurrent control, (3) no treatment concurrent control, (4) active treatment concurrent control, and (5) historical control. Sponsors are encouraged to discuss study design and selection of the control at the End-of-Phase 2 meeting with FDA.

> Sponsors are also advised to discuss with FDA their prospectively specified endpoints and methods of analysis. Sponsors should note that while the regulations state that the methods of assessing subjects' responses to an investigational therapy should be "well-defined and reliable" [21 CFR 314.126(b)(6)] and that the report of the study should include "any appropriate statistical methods" [21 CFR 314.126(b)(7)], the regulations do not specify that the sponsor or FDA is restricted to demonstrating evidence of effectiveness in accordance with a specific statistical test, a specific α value, or a specific confidence interval. Therefore, the sponsor and FDA should discuss the specific data analyses and statistical criteria at the End-of-Phase 2 meeting or Pre-NDA/BLA meeting, as appropriate.
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> Sponsors are urged to consult FDA's guidance of May 1998, entitled "*Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.*" This document provides helpful guidance to sponsors of fast track products where, in some cases, it may be appropriate to seek to demonstrate effectiveness using a single clinical trial. Other helpful information on other aspects of evidence of effectiveness are also included.

Consistent with the suggested paragraph above on controls, FDA should replace the reference on page 7 of its guidance to "principal controlled trials" with "pivotal trials" or "principal trials." For many programs for serious or life-threatening conditions, it may not be feasible or appropriate to use conventional concurrent controls. FDA should make this clear in the guidance, and avoid the use of references that could cause confusion on this point.

4. <u>Prompt Responses to Requests for Fast Track Designation</u>

FDA's guidance states (p. 9) that FDA will respond to a request for fast track designation within 60 calendar days of receipt of the request. In certain cases, FDA

should be able to respond more promptly. Most notably, when a request for fast track designation is included with the initial IND application, FDA must review the application within 30 days of receipt. In such cases, FDA should be able to respond to a request for fast track designation within 30 days as well, since consideration of the request will be interrelated with evaluation of the IND application.

5. Timely Comments on Proposed Clinical Trial Designs

FDA's guidance states (p. 11) that FDA should provide sponsors "timely comments" on the design of proposed clinical trials that will be the basis for FDA's determination of the safety and effectiveness of a product. However, the guidance provides no benchmark for what the Agency considers to be "timely comments." FDA should refer to the PDUFA II requirement that FDA provide comments within 45 days of receipt of a phase III protocol.

6. Awareness Efforts

Section 112 of the FDA Modernization Act provides that FDA shall take steps to increase awareness of the new statutory fast track program. One simple step FDA can and should take is to maintain a publicly available log of the types of products that receive fast track designation, similar to the list FDA maintains of products receiving orphan drug designation. Trade secret and confidentiality concerns would preclude identification of products and sponsors before approval; however, it would be beneficial

for FDA to maintain a list of indications receiving fast track designation without identifying any particular sponsors. Such a list would promote understanding of the Agency's fast track programs, and counter the misperception held by some that fast track development only exists for AIDS drugs.

Section 112 also provides that FDA shall "establish a program to encourage the development of surrogate endpoints that are reasonably likely to predict clinical benefit for serious or life-threatening conditions for which there exist significant unmet medical needs." Consistent with that legislative mandate, it would be extremely helpful if FDA were to issue a guidance that outlined general criteria for the development of appropriate surrogate endpoints for accelerated approval. A number of research-based companies have been actively engaged in efforts to develop surrogate endpoints, and guidance from FDA would enhance and assist those efforts.

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PhRMA appreciates the opportunity to submit these comments and looks forward to continuing to work with FDA to expedite the review and approval of new products that demonstrate the potential to address unmet medical needs for serious or life-threatening conditions.